TABLE 253-1 DIFFERENTIAL LABORATORY DIAGNOSIS OF TOXOPLASMOSIS

Clinical Setting	Alternative Diagnosis	Distinguishing Characteristics
Mononucleosis syndrome	Epstein-Barr virus infection	Serology
	Cytomegalovirus infection	Serology/PCR or culture
	HIV infection	Serology/viral load
	Bartonella infection (cat-scratch disease)	Biopsy (PCR or culture)/ serology
	Lymphoma	Biopsy
Congenital infection	Cytomegalovirus infection	Viral culture/PCR
	Herpes simplex virus infection	Viral culture/PCR
	Rubella virus infection	Viral culture/serology
	Syphilis	Serology
	Listeriosis	Bacterial culture
Chorioretinitis in immunocompetent individual	Tuberculosis	Bacterial culture
	Syphilis	Serology
	Histoplasmosis	Serology/culture
Chorioretinitis in AIDS patient	Cytomegalovirus infection	Viral culture/PCR
	Syphilis	Serology
	Herpes simplex virus infection	Viral culture/PCR
	Varicella-zoster virus infection	Viral culture/PCR
	Fungal infection	Culture
CNS lesions in AIDS patient	Lymphoma or metastatic tumor	Tissue biopsy
	Brain abscess	Biopsy and culture
	Progressive multifocal leukoencephalopathy	PCR for JC virus
	Fungal infection	Biopsy and culture
	Mycobacterial infection	Biopsy and culture

Abbreviations: CNS, central nervous system; PCR, polymerase chain reaction.

Source: Adapted from JD Schwartzman: Toxoplasmosis, *in Principles and Practice of Clinical Parasitology*. Hoboken, Wiley, 2001.

of parasites in vivo or in the identification of tachyzoites by histochemical methods. Serologic testing has become the routine method of diagnosis.

Diagnosis of acute infection with *T. gondii* can be established by detection of the simultaneous presence of IgG and IgM antibodies to *Toxoplasma* in serum. The presence of circulating IgA favors the diagnosis of an acute infection. The Sabin-Feldman dye test, the indirect fluorescent antibody test, and the enzyme-linked immunosorbent assay (ELISA) all satisfactorily measure circulating IgG antibody to *Toxoplasma*. Positive IgG titers (>1:10) can be detected as early as 2–3 weeks after infection. These titers usually peak at 6–8 weeks and decline slowly to a new baseline level that persists for life. Antibody avidity increases with time and can be useful in difficult cases during pregnancy for establishing when infection may have occurred. The serum IgM titer should be measured in concert with the IgG titer to better establish the time of infection; either the double-sandwich IgM-ELISA or the IgM-immunosorbent assay (IgM-ISAGA) should be used. Both assays are specific and sensitive, with fewer false-positive results than other commercial tests. The double-sandwich IgA-ELISA is more sensitive than the IgM-ELISA for detecting congenital infection in the fetus and newborn. Although a negative IgM result with a positive IgG titer indicates distant infection, IgM can persist for >1 year and should not necessarily be considered a reflection of acute disease. If acute toxoplasmosis is suspected, a more extensive panel of serologic tests can be performed. In the United States, testing is available at the *Toxoplasma* Serology Laboratory at Palo Alto Medical Foundation (*http://www.pamf.org/serology/clinicianguide.html*).

Molecular Diagnostics Molecular approaches can directly detect *T. gondii* in biologic samples independent of the serologic response. Results obtained with PCR have suggested high sensitivity, specificity, and clinical utility in the diagnosis of TE, and PCR technology may be becoming more readily available in resource-poor settings. Real-time PCR is a promising technique that can provide quantitative results. Isolates can be genotyped and polymorphic sequences can be obtained, with consequent identification of the precise strain. Molecular epidemiologic studies with polymorphic markers have been useful in correlating clinical signs and symptoms of disease with different *T. gondii* genotypes.

The Immunocompetent Adult or Child For the patient who presents with lymphadenopathy only, a positive IgM titer is an indication of acute infection—and an indication for therapy, if clinically warranted (see "Treatment," below). The serum IgM titer should be determined again in 3 weeks. An elevation in the IgG titer without an increase in the IgM titer suggests that infection is present but is not acute. If there is a borderline increase in either IgG or IgM, the titers should be reassessed in 3–4 weeks.

The Immunocompromised Host A presumptive clinical diagnosis of TE in patients with AIDS is based on clinical presentation, history of exposure (as evidenced by positive serology), and radiologic evaluation. To detect latent infection with *T. gondii*, HIV-infected persons should be tested for IgG antibody to *Toxoplasma* soon after HIV infection is diagnosed. When these criteria are used, the predictive value is as high as 80%. More than 97% of patients with AIDS and toxoplasmosis have IgG antibody to *T. gondii* in serum. IgM serum antibody usually is not detectable. Although IgG titers do not correlate with active infection, serologic evidence of infection virtually always precedes the development of TE. It is therefore important to determine the *Toxoplasma* antibody status of all patients infected with HIV. Antibody titers may range from negative to 1:1024 in patients with AIDS and TE. Fewer than 3% of patients have no demonstrable antibody to *Toxoplasma* at diagnosis of TE.

Patients with TE have focal or multifocal abnormalities demonstrable by CT or MRI. Neuroradiologic evaluation should include double-dose contrast CT of the head. By this test, single and frequently multiple contrast-enhancing lesions (<2 cm) may be identified. MRI usually demonstrates multiple lesions located in both hemispheres, with the basal ganglia and corticomedullary junction most commonly involved; MRI provides a more sensitive evaluation of the efficacy of therapy than does CT (Fig. 253-2). These findings are not pathognomonic of *Toxoplasma* infection, because 40% of CNS lymphomas are multifocal and 50% are ring-enhancing. For both MRI and CT scans, the rate of false-negative results is ~10%. The finding of a single lesion on an MRI scan increases the likelihood of primary CNS lymphoma (in which solitary lesions are four times more likely than in TE) and strengthens the argument for the performance of a brain biopsy. A therapeutic trial of anti-*Toxoplasma* medications is frequently used to assess the diagnosis. Treatment of presumptive TE with pyrimethamine plus sulfadiazine or clindamycin results in quantifiable clinical improvement in >50% of patients by day 3. Leucovorin is administered to prevent bone marrow toxicity. By day 7, >90% of treated patients show evidence of improvement. In contrast, if patients fail to respond or have lymphoma, clinical signs and symptoms worsen by day 7. Patients in this category require brain biopsy with or without a change in therapy. This procedure can now be performed by a stereotactic CT-guided method that reduces the potential for complications. Brain biopsy for *T. gondii* identifies organisms in 50–75% of cases. PCR amplification of CSF may also confirm toxoplasmosis or suggest alternative diagnoses (Table 253-1), such as progressive multifocal leukoencephalopathy (JC virus positive) or primary CNS lymphoma (Epstein-Barr virus positive).

CT and MRI with contrast are currently the standard diagnostic imaging tests for TE. As in other conditions, the radiologic response may lag behind the clinical response. Resolution of lesions may take